



Alert

NHS

National Patient Safety Agency

Towards the safer use of oral methotrexate



Contents

Purpose of the document	3
Executive summary	4
Introduction	5
Problems associated with the use of weekly oral methotrexate	6
Understanding the scope and causes of risk and harm associated with the use of oral methotrexate	7
Main patient safety issues identified	10
Developing and testing potential safety solutions	12
Patient information	13
Prescribing systems	15
Safe practice checklist	17
Safe dispensing practice checklist	19
Future work with pharmaceutical industry	20
Patient Safety Alert	21
Appendix 1 – Membership of External Reference Group	22
Appendix 2 – IT Requirement Specification	23

Purpose of the document

To demonstrate the thinking and process behind the oral methotrexate patient safety alert, outline the evidence for our recommendations, and provide advice for those implementing the actions within the alert.

Executive summary

The National Patient Safety Agency is improving patient safety by developing solutions to problems in medication practices. Oral methotrexate is associated with a high rate of adverse incidents and deaths in the NHS and worldwide. The efficacy of the drug is not in question and methotrexate is safe if used correctly. However, in the UK there has been a number of cases associated with oral methotrexate that have resulted in serious harm or death as a result of prescribing, dispensing, administering or monitoring incidents.

In the absence of a national database of incident reports, incident data were supplied by the NHS Litigation Authority and the medical and pharmaceutical indemnity associations to confirm the association. A literature search was undertaken of reports of incidents of patient harm associated with the use of oral methotrexate, and of local solutions proposed to prevent further occurrence.

The NPSA has worked with health professionals, patient groups, the pharmaceutical industry and medical and pharmaceutical software suppliers to identify and develop solutions.

From the information gathered, three potential solutions were identified. These included: information for the patient prior to treatment and patient-held records during treatment, improved warnings and flags for GP prescribing and pharmacy dispensing, and repackaging tablets using novel designs and in reduced quantities.

As a result of this work, the NPSA has issued a patient safety alert to the NHS for action by Medical Directors in England and Wales. This has been issued through the Safety Alert Broadcast System (SABS) in England and via direct mail in Wales. The alert asks trusts to:

- agree local action required;
- provide patient information before and during treatment;
- update prescribing and dispensing software programmes;
- review purchasing.

In March 2005 the NPSA will establish through the SABS which Trusts have and have not completed the implementation by that date. Alternative arrangements will be made for Wales. The NPSA will also seek evidence of patient outcomes through an evaluation programme.

Introduction

Methotrexate is a disease-modifying drug indicated in the treatment of severe, active, classical or definite rheumatoid arthritis, including juvenile arthritis, and severe recalcitrant psoriasis which is unresponsive to conventional therapy. For these conditions it is prescribed as a single low-dose, once a week.

It is also indicated in the treatment of neoplastic disease, such as trophoblastic neoplasms and leukaemia. For these conditions, it is prescribed orally or intramuscularly usually in daily doses. Children with acute lymphocytic leukaemia receive weekly doses of methotrexate. These conditions will normally be managed within in- or out-patient settings.

The mechanism of action in all uses is during cellular division and replication; actively proliferating tissues are susceptible to the effects of methotrexate without irreversible damage to normal tissues. Methotrexate can affect immune function.

Full blood counts, renal and liver function tests, and chest x-rays are required before treatment commences and blood tests repeated regularly (2-4 weekly) until therapy is stabilised. Thereafter it is essential that blood tests are repeated at 1-3 monthly intervals to clinically evaluate and monitor the patient, and prevent methotrexate toxicity.

When deemed clinically necessary a test dose of 5-10mg should be administered, one week prior to therapy to detect idiosyncratic adverse reactions¹. It should be used with extreme caution in older patients, and a reduction in dosage should be considered.

Prescribing data for primary care (source Prescription Pricing Authority) indicate the prescribing of oral methotrexate has continued to increase; prescribing of 2.5mg has increased by 16% during 2003, and by 64% (1998-2003), 10mg, by 8% and 121% respectively (1 year and 5 year increase).

Total annual prescribing cost to the NHS is currently in the order of £2.2million in primary care and £75,000 in secondary care.

¹ Summaries of Product Characteristics (SPCs), Medicines Compendium. 2002 ABPI, London.

Problems associated with the use of weekly oral methotrexate

Oral methotrexate is a safe and effective drug if taken at the right dose and with appropriate monitoring. However, given some of the specific requirements associated with the use of oral methotrexate, it is easy to understand why if not rigorously adhered to problems do occur. For example:

The once weekly dosage regime is unusual compared to other medicines; few medicines (5) are administered at this frequency.²

The packaging employed by the pharmaceutical industry (loose tablets in packs of 100 or blister packs of 28), resulting in re-packaging of medicines in pharmacy for patients, with the resultant loss of dose warning information (contained on manufacturers packaging), and look alike pharmacy packaging provided does not enable the patient or carer to easily identify the tablets and distinguish them from others.

Similarity of appearance between methotrexate and folic acid 5mg tablets, often prescribed concurrently, can also result in identification incidents.

Patients receiving oral methotrexate require close monitoring through clinical assessments and laboratory testing. However, there is a wide variation in the types and frequency of tests employed, leaving the patient at risk of toxicity from the drug which can be fatal.

Oral methotrexate is manufactured by or licensed to three companies within the UK. Not all brands are licensed for all conditions and therefore will only be supplied with Patient Information Leaflets (PILs) relevant to the existing licensed conditions. The pharmacist may be unaware of the condition for which the treatment has been prescribed and may consequently supply a brand not licensed for the individual patient's condition.

Manufacturer	Product	Pack size	Licensed conditions
MaynePharma	2.5mg & 10mg tablets	100	Neoplastic disease, psoriasis ³
Goldshield (Wyeth)	2.5mg tablets	28 (blister pack)	Neoplastic disease, psoriasis, rheumatoid arthritis
Pfizer (<i>brand Maxtrex</i>)	2.5mg & 10mg tablets	100	Neoplastic disease, psoriasis, rheumatoid arthritis ⁴

² Chloroquine, alendronic acid 70mg, mefloquine, mebendazole and piperazine.

³ Mayne is currently pursuing a license for RA indication for 2.5mg.

⁴ Only licensed for Rheumatoid arthritis as 2.5mg tablet preparation.

Understanding the scope and causes of risk and harm associated with the use of oral methotrexate

In the absence of data from the National Patient Safety Agency's National Reporting and Learning System (NRLS)⁵, and prior to the NPSA defining its prioritisation process, primary and secondary care medical and pharmaceutical networks were canvassed and asked to identify a 'top five' of medicines known to be associated with patient harm. Whilst the respective list each network submitted varied slightly, methotrexate was ranked highly by all as a drug which was continuously associated with patient safety incidents⁶.

Data subsequently provided by NHS Litigation Authority and the medical and pharmaceutical indemnity associations (The Medical Defence Union, Medical Protection Society, and Chemists' Defence Association), confirmed this anecdotal evidence. Collectively, 94 cases (1993-2002) which had resulted in claims against clinicians were described.

The most common reason for a litigation claim was an overdose of the drug, usually because a weekly dose had been prescribed as a daily dose, and usually by the patient's GP. The causes behind these are slightly more complex but briefly comprised:

- ambiguous or unclear letters from specialists (or their representatives) to GPs including starting dose, increasing dose, frequency and type of monitoring required;
- continuation of drug treatment after cessation by the specialist;
- failing to perform the required regular blood tests;
- delayed receipt of results of blood tests, or failing to alter medication after receiving abnormal results;
- computer errors:
 - accidentally selecting once daily for 'as directed' or 'weekly'; and
 - repeat prescribing without regular monitoring;
- not checking prescriptions written by others before signing;
- prescribing after telephone consultations with specialists;
- not following prescription and monitoring protocols (shared care guidelines) when present, or no protocols available;
- not accounting for prescribing in older patients, those with impaired renal or hepatic function or those on concurrent folate antagonists;
- pharmacists not checking dosages before dispensing;
- pharmacists not dispensing the correct medicine or correct strength of tablet.

⁵ NRLS was launched in February 2004, although a very small volume of data (9 incidents involving methotrexate) were available from the pilot stage.

⁶ Patient Safety Incident definition; any unintended or unexpected event, in NHS funded care, which led to variable degrees of harm, from none to death, to one or more patients.

These data obviously only relate to incidents of harm when the patient or their family or representative(s) have then pursued litigation against the clinician involved. They are therefore only the tip of the iceberg, with an unknown volume of incidents predominantly unrecorded.

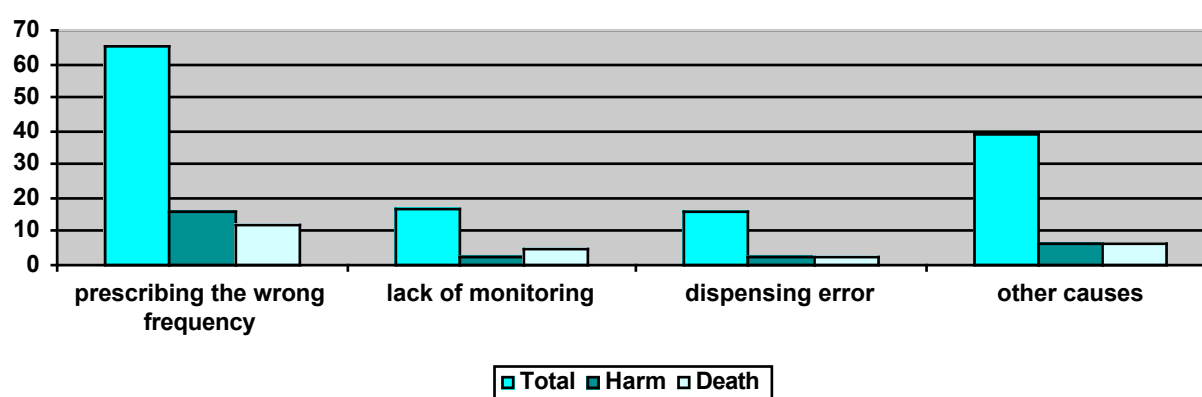
A literature search was also undertaken of reports of incidents of patient harm associated with the use of oral methotrexate, and of published guidelines and recommendations to minimise risk in its use. International papers were included within the search (i.e. it was not restricted to UK-only papers) in order to consider and compare approaches adopted (if any) by other countries or health organisations.

A search was made of the following: Cochrane Reviews, Bandolier, MEDLINE PubMed, ISMP, National Electronic Library for Health, Google, using the keywords methotrexate, methotrexate prescribing, methotrexate error, medication error, errors.

Combining the anecdotal information, litigation claims and literature review for UK-based incidents, a total of 137 incidents were identified, of which 25 had resulted in the death of the patient, and 26 in serious harm requiring hospitalisation, see Figure 1.

Similar problems were identified in the American, European and Australian literature.

Figure 1 Errors and outcomes described within peer reviewed literature and by professional insurance/defence associations



The Cambridgeshire incident

Prior to the initiation of the NPSA's work, an Panel of Inquiry into the death of a patient due to incorrect prescribing of methotrexate reported its findings in July 2000⁷. The inquiry found that an error on a prescription which increased the patient's dosage was perpetuated inadvertently by a number of different people involved in the patient's care.

The Panel of Inquiry made a number of strong recommendations, including ensuring:

- there is sufficient time to explain to a patient and any carers about any changes in medication;
- that GP and pharmacy systems are programmed to flag up warnings when potentially toxic drugs like methotrexate are prescribed or dispensed;
- that GPs have access to a patient's records during house calls and out of hours consultations (ideally by the development of patient-held records);
- that record keeping and record amendment is rigorously maintained in GP surgeries, pharmacies and hospitals.

In addition the Panel of Inquiry recommended that the Department of Health be encouraged to discuss the safety aspects of the drug with the manufacturers.

An audit undertaken by the Cambridgeshire and Peterborough Public Health Network in April 2002⁸ to monitor local progress against the recommendations of the inquiry concluded that some had been implemented, but there was "still much to do if these recommendations are to be implemented fully".

Whilst the local community had undoubtedly begun to deliver safer care, it was evident that some recommendations were centrally related in that they could only be best done at a national level.

⁷ Methotrexate Toxicity. An Inquiry into the Death of a Cambridgeshire Patient in April 2000. Cambridgeshire Health Authority, July 2000.

⁸ Methotrexate Audit. Kelvin Rowland-Jones, Community Audit Facilitator. Cambridgeshire & Peterborough Public Health Network, hosted by Huntingdonshire PCT, April 2002.

Main patient safety issues identified

In order to confirm the findings of the data collection and the main patient safety issues to be addressed at a national level, a project approach was applied.

An External Reference Group was established. This group comprised rheumatology and dermatology specialist and generalist medical, pharmaceutical and nursing clinicians from primary and secondary care, and representatives from the relevant Royal Colleges and Royal Pharmaceutical Society (for membership, see Appendix 1).

Patients and members of the public were also consulted. Contacts were established through registered charitable groups covering the clinical conditions for which methotrexate is indicated. Some patients and carers were also recruited through personal contact following specific safety incidents reported to the NPSA. A virtual group was formed, mainly due to the inability of some individuals to attend daytime meetings at a centralised location. Instead, individuals were contacted by telephone and semi-structured interviews were conducted.

Patient comment on tablet appearance:

“I do think it unfortunate that the 2.5mg and 10mg tablets are almost identical in appearance and size... The only solution would seem to be to make the 10mg and 2.5mg tablets in different colours and/or to make them very different in size and shape.”

Patient comment on dosing frequency:

“When I was first prescribed methotrexate, it was stressed both orally and in writing regarding the fact that it was to be taken weekly, as a lady in our area had just recently died due to taking it daily. This scared me quite a lot as I realised how potentially dangerous this drug could be, and so was extremely worried about using it. I found myself checking the bottle label several times and counting the tablets several times too prior to taking them. I often got my husband to check it with me as well.”

Patient comment on packaging:

“To me it just seems bizarre why you’d give someone with arthritis a bottle that is hard to open. It’s kind of like saying: ‘Here’s your medication...if you can get into it!’”

Patient comment on information:

“Without actually naming the consultant, I had very little information about it, really... I’m not sure he mentioned it. I think you just pick it up from the bottle... Whatever it says on the bottle is what you tend to do.”

A safe medication pathway was described, and populated with the incident information (Figure 2). Besides depicting a safe route this served to identify the critical stages in the pathway by employing a simple risk assessment process: likelihood of occurrence versus severity of outcome for the patient. Finally, it was utilised as a robust and impartial tool to predict potential safety solutions for development.



Developing and testing potential safety solutions

The key findings emanating from the early consultation were that for safe medication practice the following were required:

- better informed patients (and timeliness of information provision);
- better informed and supported clinicians;
- clarity of monitoring and responsibilities;
- easily distinguishable packaging with clear warnings.

Due to the diverse nature of the findings, no one solution was available to prevent future dosing errors with oral methotrexate. Consequently, three potential solutions were identified, each of which would prevent some opportunity for harm, and collectively would prevent or reduce all harm based upon the causal and contributory data available at the time.

- 1 information for the patient prior to commencement of treatment and patient-held records post commencement which included monitoring schedules and results;
- 2 improved warnings and flags for GP prescribing and pharmacy dispensing IT systems which were not easily over-ridden;
- 3 repackaged tablets using novel designs and in reduced quantities so that the patient receives the original manufacturers pack.

Patient information

Through the collaboration of the External Reference Group and the patient and public representatives, several information resources were proposed for testing and development:

- a a treatment initiation checklist for the specialist to confirm all information is provided and baseline tests conducted prior to treatment commencement;
- b a leaflet for the patient to read before commencing treatment and which describes the benefits and risks of the tablets; and
- c an information and recording diary in which patients can store all information about their administration routine, notes to discuss with clinicians, and their monitoring blood test results.

The documents contained all the main issues patients (and their carers) need to be aware of, whilst seeking to strike a balance between highlighting the risks and benefits of the treatment, and were presented in an easy to understand format.

Much of the content was derived from existing sources of nationally and locally available information.

The products were tested by several different cohorts using differentiated questionnaires to elicit feedback from the respective groups:

- 1 patient representatives as before (current and previous methotrexate patients or carers);
- 2 new patients receiving methotrexate for the first time from their rheumatology or dermatology specialist consultant;
- 3 juvenile arthritis patients currently receiving methotrexate;
- 4 patients with existing arthritic conditions but who have never been prescribed methotrexate – a quasi control group who were familiar with the clinical conditions and impact that these had upon their lifestyles.

Relevant Royal Colleges and Societies, and professional insurance and indemnity organisations also provided comments using similarly adapted questionnaires.

A note of caution on this methodology⁹; using questionnaires to elicit information from patients requires patients to have a good level of literacy and might therefore exclude some patients.

Patients who were not currently prescribed methotrexate, but who had received it in the past, at times felt unable to contribute to the project.

Conversely, patients who have been prescribed methotrexate for a significant period had acquired a high level of understanding about the associated risks. As a result, they

⁹ Note: All testing and evaluation undertaken directly with patients have been conducted under Local Ethics Research Committee agreements. This applies to the patient-held information, and the observational studies for packaging and labelling functionality.

found it difficult to evaluate patient information and be objective about the products designed.

Despite best efforts, a narrow and homogenous profile existed within the test group.

Top-line evaluation results

Patients should be given information about oral methotrexate and allowed time to understand it or discuss it with their families, before embarking on treatment. This information should be provided in useable formats and in language that they can comprehend. The weekly dosing regime and the importance of monitoring must be stressed.

Small changes were required to be made to the leaflet following the feedback. It should be promoted as an information tool to support patients in informed decision making prior to commencement of treatment.

A checklist for positive practice indicators should be developed from the original treatment initiation checklist, to also include specific detail on shared care guidelines and monitoring responsibilities.

Significant changes were required to be made to the diary based upon the feedback. The document must serve three key purposes:

- provide detailed information about methotrexate, how to use it safely, what to be aware of, and suggested lifestyle advice;
- an aide memoire to weekly administration and to monitoring schedules;
- a record of test results.

A diary format is not required.

A change in format has the dual advantage of making the document significantly shorter, (and therefore more economical to produce), and giving it a greater shelf-life (making sustainability across the service a less significant factor).

Templates for the core information content, and typographical layouts, are included within the alert for the two resulting documents. These can be adapted to contain localised information such as telephone help-lines, or clinic opening times. Copies should be made available to all relevant rheumatology and dermatology clinics and hospital pharmacies for provision to patients. Copies should also be circulated to general practitioners and community pharmacists for information and familiarisation so that they too may make relevant entries in to the record when necessary.

Prescribing systems

Risk assessments were conducted with the two major database providers for UK prescribing and pharmacy systems: EMIS and FDBE¹⁰. The critical stages of data entry or user selection were identified through a risk matrix (likelihood of occurrence versus severity of outcome) and a specification for change built upon these events for safety solution development.

Critical stages were identified at:

- drug selection (including form and strength) – users relied upon minimum first three letters in a drug name to produce a pick list;
- on selection of methotrexate, a small icon or text box appeared stating 'Cytotoxic'. Some surgery staff involved with repeat prescription issue did not understand this nor react to it;
- due to the multiplicity of licensed use, the frequency of dose has not been locked down as a default or setting which could not be over-ridden, thereby allowing daily or multiple dosing to be prescribed unchallenged;
- all systems allowed dual therapy to be prescribed e.g. simultaneous prescribing of tablets and sub-cutaneous injection;
- some systems allowed a prescription to be generated too frequently i.e. before the next repeat prescription was due based upon previous date and quantity of tablets supplied;
- whilst some systems provide clinical information in the background, none link prescribing to clinical monitoring i.e. blood test results and prescription are not linked.

The solution IT specification briefly comprised:

The presentation of the picking list should distinguish between 'high alert' and 'non-high alert' drugs. Based upon *National Programme for IT Style Guide*, it should do so in the following ways:

- the words 'High Alert', 'Alert' or 'Toxic' must appear in front of the drug name;
- it needs to be distinguishable with an icon and displayed in red;
- all high alert/toxic drugs appear grouped at either the end (preferable), or the beginning of a picking list.

¹⁰ Legal advice has been taken where testing and evaluation have been undertaken with commercial companies to ensure transparency and equity of approach. This applies to the pharmaceutical industry and the prescribing and pharmacy software systems suppliers.

When methotrexate is selected the system will display an additional user message reminding the GP that the dosage is weekly rather than daily. It will appear in the centre of the screen.

It should state:

This is a NPSA High Risk Process

Confirm you have selected methotrexate tablets at strength xx mg.

<button>: Proceed. If selected, the users' support system is invoked to prescribe the drug.

<button>: Do not proceed. If selected, the user is returned to the screen prior to this secondary alert.

The functionality should be simple, specifically, that the picking list should standardise the dosing prescribing/administration options for methotrexate tablets.

Full IT specification details can be found in Appendix 2.

Changes to all prescribing software programmes should be completed by all software system suppliers by November 2004. By March 2005 all system users must have implemented the up-date provided by their respective suppliers.

It is recommended that pharmacies also implement the same requirements within their systems by March 2005. Those using systems using the Multilex Drug Data File will be able to request from FDBE the necessary data changes, documentation and toolkits. Pharmacy systems not covered by this procedure are the responsibility of the individual trust, company, individual pharmacist or dispensing doctor and it is recommended that all seek to apply the specification in Appendix 2.

Safe practice checklist

During the testing and development phases of the various elements of the solutions, it became readily apparent that clinical practice varied significantly across the NHS.

This was particularly evident through a plethora of local shared care guidelines and general inconsistency toward monitoring responsibility. The guidelines are predominantly focused upon transfer of prescribing from secondary care specialist to the primary care GP, and neither the guidelines nor the specialists' discharge letters contain explicit instructions regarding monitoring schedules, responsibility for conducting the monitoring tests and review of results, including action to be taken if results are outside of the norm.

Similarly, guidance on the length of period for supply between blood testing, and communication of changes in dosage directions were also found to be lacking.

Following discussions with the relevant clinical groups and organisations, a checklist for positive practice was proposed to provide a consistent approach.

Safe prescribing practice checklist

- Initiating treatment; information is available to provide to the patient on the risks and benefits of this medicine, confirmation of patient understanding/consent, baseline tests conducted, monitoring need and schedule explained to patient. Patient-held recording document issued and use explained.
- Issues to be addressed within Shared Care Guidelines – clarity of prescribing and monitoring responsibilities. How often will blood tests be conducted and in which location. Which clinician will be responsible for receipt and review of the results, and who will communicate necessary dosage changes to the patient (and to GP if hospital reviewed for GP prescriber). Who will record test results in to the patient-held record document.
- Trusts without Shared Care Guidelines must make similar appropriate arrangements. The British Society for Rheumatology has published guidelines for the monitoring of disease modifying drugs including methotrexate, and which may be a useful source of information.
- All prescribers should avoid the use of 'as directed' in prescribing – a specific dose must be applied to each prescription. Patients often understand their dose by number of tablets rather than 'mg'; quantity and frequency of dose should be regularly discussed with the patient.
- Repeat prescriptions should be removed from the surgery repeats pile and retained separately for prescriber review prior to authorising by signature. Changes to printer driver software to shade prescription signature space on FP10 / WP10 to alert prescriber to high risk drug might also help in this instance.

- Beware patients attending with other symptoms; signs of methotrexate toxicity or intolerance may present as for example, breathlessness, dry persistent cough, vomiting and diarrhoea.
- Patients receiving methotrexate may be admitted to any ward or receive outpatient treatment for co-existing conditions, and staff in all areas may therefore be involved in continuity of prescribing, monitoring or administering methotrexate as a result. Full medication reviews, conducted by pharmacists, should be undertaken on admission and prescribing, monitoring and administration requirements recorded in the patients notes.
- It is the prescribers responsibility to record the correct dosage and frequency on the hospital drug administration chart, and to strike out the six days of the week when a dose must not be administered in the administration section on the chart.
- Handwritten prescriptions and discharge summary information must be complete and legible and include in full the form, strength, dose and directions.

Safe dispensing practice checklist

- Request sight of the patient-held recording document and check if any dose changes have been made since last prescription issue; this is to double check in case prescribing systems have not been up-dated post test review.
- Assessment of need of individual patients; packaging, labelling and PIL requirements for patients who may have reduced manual dexterity. Larger containers, or ribbed easy-to-grip lids may remove the likelihood of patients decanting the tablets into a jam jar once at home.
- The strength of tablet supplied to the patient must remain consistent to prevent any confusion for the patient over the number of tablets they need to take.
- Communicate the dose as quantity of tablets and weekly frequency to the patient. Is a dose reminder required e.g. patient administration record sheet.
- Differentiation between methotrexate and folic acid packaging. If patients receive both medicines concurrently how can they distinguish between them given that both may be round yellow tablets of similar size? The packaging can offer a clue, so needs to differ for the two medicines.
- Beware patients attending with other symptoms; signs of methotrexate toxicity or intolerance may present as for example, breathlessness, dry persistent cough, vomiting and diarrhoea. Know when to refer back to the prescriber. It is good practice to maintain a record of OTC items supplied to the patient.

Future work with pharmaceutical industry

The pharmaceutical industry has recognised the difficulties experienced by patients (and clinical staff) in distinguishing between the two strengths of the tablets, and has already made licensed changes to the 10mg tablet shape.

A buy-back procedure has also been implemented to remove all 'old shape' 10mg tablets from circulation (MHRA Drug Alert EL(04)A/04).

In March 2003, following a review by the Committee on Safety of Medicines, MHRA issued guidance on labelling and packaging¹¹. This included a warning that manufacturers' packs of methotrexate should contain a critical warning of:

'Check dose and frequency – Methotrexate is usually taken once a week'

However, replication of this critical warning is not regularly utilised on pharmacy labels when re-dispensed from bulk containers.

A study was commissioned to identify the needs and functionality for safe administration of oral methotrexate¹². Key findings underscored the importance of the other solutions in reducing dosing errors with methotrexate, and also demonstrated that the design of the present packaging and labelling made demands which were inappropriate for the typical needs and abilities of methotrexate patients.

Work is therefore continuing with the pharmaceutical industry to develop or adapt packaging designs which maintain pharmaceutical integrity and efficacy, and which are clear, distinctive, and accessible to users. At the same time, changes to the quantity of tablets contained within the packaging will be made, based upon Prescription Pricing Authority Q-data, to reduce the pack sizes to meet 85-90% of all primary care prescriptions. This will remove the need for pharmacy to re-pack the tablets – and which can be reinforced in the future through default settings to GP prescribing systems to the patient pack quantities.

¹¹ MHRA Best Practice Guidance on the Labelling and Packaging of Medicines, March 2003.

¹² The packaging and labelling of solid oral medicines. A study to identify the needs and functionality for safe administration of solid oral medicines using oral methotrexate as an example. A report to the National Patient Safety Agency, April 2004. Engineering Design Centre, University of Cambridge and Robens Centre for Health Ergonomics, University of Surrey.

Patient Safety Alert

Introduction to the alert

Oral methotrexate is a safe and effective medication if taken at the right dose and with appropriate monitoring. However, 25 patients have died and 26 have been seriously harmed in the last ten years in England alone due to problems with taking the medication. Two thirds of all incidents result from the wrong dose being prescribed and a fifth are linked to poor monitoring.

The NPSA has developed solutions to help NHS organisations reduce the risk faced by patients taking this medication.

Evaluating the alert

By March 2005 the NPSA expects trusts to have implemented the standardised patient information and patient-held monitoring documents, and where IT systems currently exist to have worked with the relevant clinical groups to ensure up-dates to the software are applied.

Where IT systems are planned in the future, the warnings should be included within the programme specification.

Where these have not happened, the NPSA will expect the relevant Strategic Health Authority or Regional Office to provide a full explanation of the reasons.

In March 2005, the NPSA will establish through the Safety Alert Broadcast System (SABS) which trusts have and have not completed the implementation by that date. Alternative arrangements will be made for Wales. This will provide evidence of change.

To provide evidence of outcome, NPSA will:

- 1 undertake a routine monitoring request for 'methotrexate' within National Reporting and Learning System (NRLS) data;
- 2 conduct an audit of IT prescribing and dispensing system suppliers to confirm the IT changes have been (i) applied, and (ii) screen shots appear as described;
- 3 monitor primary care prescribing trends from Prescription Pricing Authority (PPA) Q-data;
- 4 review secondary care prescribing through a survey conducted in hospital pharmacies;
- 5 monitor the availability of easily distinguishable tablet forms (i.e. both strengths of different shape) by regular contact with MHRA to confirm license agreements held by any companies (existing and new manufacturers or importers);
- 6 follow up SABS responses to request random example copies of the patient-held documents.

Appendix 1

Membership of External Reference Group

Dr Christopher Kelsey, Consultant Rheumatologist, and also representing the Royal College of Physicians

Dr Allan Marsden, British Association of Dermatologists, replaced during 2003 by Dr Jane Sterling, Assistant Honorary Secretary, British Association of Dermatologists

Dr Robert Chalmers, Consultant Dermatologist

Dr Maureen Baker, NPSA Director of Primary Care, and Honorary Secretary Royal College of General Practitioners

Janice Mooney, Chair of RCN Rheumatology Forum, and representing the Royal College of Nursing

Catherine Dewsbury, Clinical Governance Pharmacist, and representing the Royal Pharmaceutical Society of Great Britain

Narinder Bhalla, Clinical Governance Pharmacist Addenbrookes Hospital

Brit Cadman, Hospital pharmacist, and also representing the Guild of Healthcare Pharmacists

Michelle Styles, Head of Information Services, National Pharmaceutical Association

Steve Eastham, representing the Company Chemists Association

Observers:

Dr Julie Williams, MHRA

Appendix 2

IT Requirement Specification

Methotrexate Alerts

Synopsis

This document sets out the requirements for addressing methotrexate-related patient safety incidents (PSI) that occur in general practice. It specifically focuses on why GPs mis-prescribe methotrexate and how the GP [prescribing decision] support systems can be enhanced to minimise the risk of further errors occurring.

In fulfilling the above objective this project will also set a framework for promoting a synergy between patient safety and technology. The project aims to comply with the National Programme for IT in such a way that it is structured and repeatable.

Summary of Contents

1	Overview of requirements	25
1.1	Out of scope	25
1.2	In scope	25
2	Point of drug selection	26
2.1	Distinguishing toxic drugs	26
2.2	Initial alert	27
2.3	Standardising dosage	28
2.3.1	Non-standard dosage	28
2.4	Avoiding prescribing errors: dual therapy	28
2.5	Avoiding prescribing errors: premature repeat prescription	28
2.6	Other GP support systems	28
3	Compliance with standards and points for review	29

Document references

Document Name.	Release Date	Author	Comment
Common User Interface Project – Style Guide Sample Sections v1	11 December 2003	M. Bainbridge	NPfIT Draft for comment

1 Overview of requirements

The scope of this requirement specification is limited to one of the objectives to reduce or remove harm associated with dosing errors with oral methotrexate, namely, changes to GP support systems to flag methotrexate alerts and prevent erroneous prescribing.

It seeks to address the central concern that methotrexate is a toxic drug with unusual dosing. Over a period of 10 years (1993 – 2002) there were 137 cases in England, of which there were 25 patient deaths and 26 cases of serious, long-term harm associated directly with the use of oral methotrexate tablets. Sixty seven percent of these cases were due in whole or part to overdose of the drug because a daily dose had been prescribed usually by the patient's GP.

1.1 Out of scope

Rollout of the software to GPs and other customers of the suppliers is not in scope. This project will be complete when a 'shrink-wrapped' package has been delivered to the GP suppliers.

1.2 In scope

This project will deliver a 'shrink-wrapped' package to the system suppliers that will be sufficiently easy to implement such that it will have an insignificant impact on their development resources. The enhancement/development of the EMIS and FirstDataBank¹³ drug databases are within scope of this project:

EMIS also support the following GP systems	
EMIS LV (text-based system) ¹⁴ Primary Care Systems (PCS) ¹⁵	GV
FirstDataBank provides its Multilex Drug Data File (Multilex DDF) to the following GP System Suppliers.	
Torex Health In Practice Systems Seetec Protechnic Exeter Microtest Phoenix Partnership Health One	Healthy Software Chime/TCR Systems Solutions OXA Adastra CSE-Servelec

In outline, the principle requirements of a solution are that it has:

- picking list options; drug form and strength;
- alerts: timely, appropriate, not overridden;
- barriers: dual therapy, frequency of issue;
- clinical audit and monitoring.

¹³ Unlike EMIS, FirstDataBank do not supply a computer system but a medicine database which is integrated into the above systems.

¹⁴ For further information see <http://www.emis-online/lv.asp>

¹⁵ EMIS plan to move both LV and GV clients to PCS

2 Point of drug selection

2.1 Distinguishing toxic drugs

A number of GP support systems offer a picking list of drugs. The presentation of the picking list should use the following style guide. The ‘*Penicil*’ example has been used here to demonstrate the distinction between ‘high alert’ and non-high alert drugs. The primary objective in this graphic is to distinguish toxic from non-toxic drugs. It does so in the following ways:

- the word ‘High Alert’, ‘Alert’ or ‘Toxic’ must appear in front of the drug name;
- it needs to be distinguishable with an icon and displayed in red. The NPSA accept that colour might not be achievable initially for some systems;
- all high alert/toxic drugs appear at either the end (preferable), or the beginning of a picking list;
- when selected system will display an additional user message. The display and content of this message will be dependent on the specific drug e.g. selection of methotrexate would display a message reminding the GP that the dosage is weekly rather than daily.

The screenshot shows a 'select medication' window with a search bar containing 'penicil'. Below the search bar is a table of drug formulations. The table has columns for NHS status, In Stock status, Drug Formulations (Generic), £Min, and Pack. The first three rows are for Penicillin V formulations. The last two rows are for High Alert Penicillamine formulations, which are marked with a red exclamation mark icon and red text.

NHS	In Stock	Drug Formulations (Generic)	£Min	Pack
NHS	Yes	Penicillin V 250mg Tablets	0.35	28
NHS	Yes	Penicillin V 125mg/5ml Elixir	0.22	30
NHS	No	Penicillin V 250mg/5ml Elixir	0.39	14
NHS	Yes	⚠ High Alert Penicillamine 125mg Tablets	0.28	56
NHS	Yes	⚠ High Alert Penicillamine 250mg Tablets	0.28	56

At the bottom of the window, there are radio buttons for 'Generic name' (selected) and 'Proprietary name', and 'OK' and 'Cancel' buttons.

Figure 1.3 - Example drug formulations list with Toxic drugs¹⁶

¹⁶ This graphic is drawn from *Common User Interface Project - Style Guide Sample Sections v1: National Programme for IT*. It is used here to illustrate how toxic drugs are distinguishable from others. It is *not* intended to fix the design at this stage. The design will be fixed in later versions of this document released by NPfIT.

2.2 Initial alert

When methotrexate is selected the system will display an additional user message. The display and content of this message will be dependent on the specific drug e.g. selection of methotrexate would display a message reminding the GP that the dosage is weekly rather than daily. The graphic displayed should use the following style guide.

It will appear in the centre of the screen.

It should state:

This is a NPSA High Risk Process

- *Confirm you have selected Methotrexate tablets at strength xx mg*
- **<button>: Proceed.** If selected, the users support system is invoked to prescribe the drug.
- **<button>: Do not proceed.** If selected, the user is returned to the screen prior to this secondary alert.



Figure 4 - Initial alert

2.3 Standardising dosage

In the short-term the functionality should be simple, specifically, that the picking list should standardise the dosing prescribing/administration solutions for methotrexate tablets.

The standard dosages are as follows:

Methotrexate tablets 2.5mg:	Methotrexate tablets 10mg:
2.5mg (one tablet) to be taken weekly	10mg (one tablet) to be taken weekly
5mg (two tablets) to be taken weekly	20mg (two tablets) to be taken weekly
7.5mg (three tablets) to be taken weekly	(No dose greater than 20mg will be presented for the 10mg dose)

2.3.1 Non-standard dosage

It should be possible, but not easy, to over-ride these dose options to prescribe greater multiples of 2.5mg, as some localities have chosen to use one strength, 2.5mg, of the tablet. It is recommended that the user is prompted to record clinical evidence of over-ridden dosages.

It should only be possible to prescribe a daily dose in *exceptional* circumstances. Again, the user should be prompted to record clinical evidence to support this change.

2.4 Avoiding prescribing errors: dual therapy

It is currently possible to prescribe two forms of methotrexate simultaneously. Except in very rare situations, this is undesirable. The NPSA specifically wishes to prevent the prescribing of methotrexate by either two different routes (oral and SC) or two different formulations (tablets and injection) at the same time. From what is stated above the functionality would warn if a physician prescribed both 2.5 and 10mg tablets. FDBE has functionality already to alert to duplicate ingredient prescribing. Multilex DDF has coded ingredient and both base formulation and routes. The dual therapy may occur as a result of an error and so an alert of the sort described in paragraph 2.2 should be displayed asking the user to confirm. If it is not then the user is returned to the previous screen.

2.5 Avoiding prescribing errors: premature repeat prescription

This requires interaction with the individual patient history record held on the GP system.

Some GP systems contain a field for 'Number of Repeats' or 'Frequency of Repeats'. If possible, the GP system would recognise a repeat for methotrexate and display a corresponding alert if the prescription were to be generated more than one month before the previous prescription supply should have been exhausted.

2.6 Other GP support systems

The remainder of GP support systems that do not offer a picking list of drugs will, it is expected, change in line with standardisation through the National Programme for IT.

3 Compliance with standards and points for review

All above proposals have been subject to a risk assessment to ensure that the end products are intuitive, reasonable, and do not lead to additional or new error.

Publications issued by the NPSA



Alert

A **patient safety alert** requires prompt action to address high risk safety problems



Notice

A **safer practice notice** strongly advises implementing particular recommendations or solutions



Information

Patient safety information suggests issues or effective techniques that healthcare staff might consider to enhance safety

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